Glycemic index, glycemic load, and risk of coronary heart disease: a pan-European cohort study

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ABSTRACT

Background: High carbohydrate intake raises blood triglycerides, glucose, and insulin; reduces HDLs; and may increase risk of coronary heart disease (CHD). Epidemiological studies indicate that high dietary glycemic index (GI) and glycemic load (GL) are associated with increased CHD risk.

Objectives: The aim of this study was to determine whether dietary GI, GL, and available carbohydrates are associated with CHD risk in both sexes.

Methods: This large prospective study—the European Prospective Investigation into Cancer and Nutrition—consisted of 338,325 participants who completed a dietary questionnaire. HRs with 95% CIs for a CHD event, in relation to intake of GI, GL, and carbohydrates, were estimated using covariate-adjusted Cox proportional hazard models.

Results: After 12.8 y (median), 6378 participants had experienced a CHD event. High GL was associated with greater CHD risk [HR 1.16 (95% CI: 1.02, 1.31) highest vs. lowest quintile, p-trend 0.035; HR 1.18 (95% CI: 1.07, 1.29) per 50 g/day of GL intake]. The association between GL and CHD risk was evident in subjects with BMI (in kg/m^2) $\geq$25 [HR: 1.22 (95% CI: 1.11, 1.35) per 50 g/d] but not in those with BMI <25 [HR: 1.09 (95% CI: 0.98, 1.22) per 50 g/d) (P-interaction = 0.022). The GL–CHD association did not differ between men [HR: 1.19 (95% CI: 1.08, 1.30) per 50 g/d] and women

[HR: 1.22 (95% CI: 1.07, 1.40) per 50 g/d] (test for interaction not significant). GI was associated with CHD risk only in the continuous model [HR: 1.04 (95% CI: 1.00, 1.08) per 5 units/d]. High available carbohydrate was associated with greater CHD risk [HR: 1.11 (95% CI: 1.03, 1.18) per 50 g/d]. High sugar intake was associated with greater CHD risk [HR: 1.09 (95% CI: 1.02, 1.17) per 50 g/d].

Conclusions: This large pan-European study provides robust additional support for the hypothesis that a diet that induces a high glucose response is associated with greater CHD risk. *Am J Clin Nutr* 2020;112:631–643.

Keywords: glycemic index, glycemic load, coronary heart disease, cohort study, EPIC study, EPIC-CVD study

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Supplemental Figure 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Data described in the article, code book, and analytic code will be made available upon request pending application (http://epic.iarc.fr/access/index.php).

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Abbreviations used: CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; GI, glycemic index; GL, glycemic load; SSB, sugar-sweetened beverage.

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Introduction

Dietary guidelines have long emphasized that reducing consumption of fat, particularly saturated fat, and getting more calories from unsaturated fat or carbohydrate lower risk of cardiovascular disease (CVD), including coronary heart disease (CHD) (1). Conversely, evidence from observational studies suggests that replacing saturated fat with sugars or refined starch does not reduce risk but, rather, may increase it (1, 2); replacing fat with carbohydrates from whole fruits, vegetables, pulses, and whole grains may decrease risk (3).

High intake of carbohydrates, particularly refined carbohydrates, can raise fasting triglycerides (4), reduce HDLs (5), and increase blood glucose and insulin (6). It may also increase CHD risk.

Variation in the ability of carbohydrates to increase blood glucose is captured by the glycemic index (GI) (7), which ranks carbohydrate foods according to their blood-glucose-raising ability. Dietary GI is a measure of the overall ability of consumed carbohydrates to raise blood glucose. Glycemic load (GL), the product of a food's GI and its available carbohydrate, incorporates the effect of the total amount of carbohydrate consumed (7). Dietary GL is the sum of the GLs for all carbohydrate-containing foods consumed, and it reflects the quantity as well as the blood-glucose-raising ability of consumed carbohydrates.

Reviews and meta-analyses on GI/GL and CHD risk (8–11) found that high GI and GL diets were associated with increased CHD risk in women, especially women with high BMI (in kg/m^2), but in men findings were inconsistent. A 2019 meta-analysis of prospective studies found that high dietary GI and GL were strongly associated with increased CHD risk in both sexes (12). However, a large and comprehensive 2019 review and meta-analyses on carbohydrate quality and several noncommunicable disease endpoints, including CHD, reported that across observational studies and clinical trials, GI had no or inconsistent association with CHD, whereas high GL was moderately associated with increased CHD risk (13).

We estimated associations between risk of first CHD event and dietary GL, GI, and available carbohydrate in a large pan-European cohort of men and women recruited to the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Methods

Study population

EPIC is a prospective study of ∼520,000 men and women, mostly aged 35–70 y, recruited between 1991 and 1999 from 23 centers in 10 European countries: Denmark, France, Greece, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. Details of EPIC design and methods are described elsewhere (14). Briefly, volunteers completed dietary and lifestyle questionnaires, and their anthropometric measurements were recorded by trained health professionals (self-reported in France, Norway, and Oxford, UK); most also provided blood samples. All participants gave written informed consent. Ethical committees of the International Agency for Research on Cancer and local centers approved the EPIC protocol.

After exclusion of 10,455 with a history of myocardial infarction or stroke, 44,318 with a history of diabetes, 6837 with no dietary data, and 7412 in the top or bottom 1% of the ratio of energy intake to energy requirement, 452,752 remained. After also eliminating participants from France and Norway for incomplete follow-up and 2254 cases whose date of CHD diagnosis was before the date of EPIC baseline (prevalent cases), a total of 338,325 participants remained, including 6378 CHD incident cases (**Supplemental Figure 1**).

Measurements

First fatal and nonfatal CHD events were defined by codes 410–414 of the 9th edition or I20–I25 of the 10th edition of the International Classification of Diseases. EPIC centers identified events by various methods, including primary and secondary care databases, hospital admissions records, and self-report (15). Nonfatal CHD events were validated from medical records or databases. Fatalities were usually confirmed from mortality databases. End of follow-up varied with center: from end of 2003 to end of 2010.

Diet throughout the year up to recruitment was assessed by country-specific (in some cases center-specific) questionnaires designed to capture local eating habits. Nutrient values of consumed foods were obtained from the EPIC Nutrient Database (16). Published values of GIs (glucose as reference) (17–19) were assigned to carbohydrate-containing foods as described elsewhere (20).

Average dietary GI for each participant was calculated as the sum of the GIs of each food item consumed, multiplied by the average daily amount consumed and percentage carbohydrate content, all divided by the total daily carbohydrate intake. Dietary GL was calculated similarly except that there was no division by daily carbohydrate intake.

A standardized lifestyle questionnaire at recruitment recorded menopausal status, hormone treatment, medical history, physical activity, alcohol consumption, smoking, education, and other information. Weight and height were measured at recruitment, except in France, the Oxford center, and Norway, where they were measured in a subset and self-reported in the rest. Physical activity was categorized according to the Cambridge Physical Activity Index (21).

Blood pressure was measured using standard procedures, but it was only available for 62% of participants (22). We therefore used a composite blood pressure variable available for 92.4% of participants: if 1 or more of self-reported hypertension, self-reported use of antihypertensive medication, systolic blood pressure >140 mm Hg, and diastolic blood pressure >90 mm Hg were present, the participant was considered hypertensive. Other categories were normotensive or unknown/missing (7.6%).

Circulating CHD risk factors were available for a subcohort of 18,157 EPIC participants randomly sampled from all 23 EPIC centers, with stratification by center (23). The following factors were measured: high-sensitivity C-reactive protein (CRP), total cholesterol, HDL cholesterol and triglycerides (Stichting Huisartsen Laboratorium), erythrocyte glycated hemoglobin (G8 HPLC analyzer; Tosoh Bioscience), and glucose (Cobas enzymatic assay; Roche Diagnostics). Because LDL cholesterol was not directly assayed, non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol.

Statistical methods

Participant characteristics are presented as means ± SDs (continuous variables), or percentages (categorical variables), by quintiles of energy-adjusted GI and GL. Primary outcome variables were HRs for CHD in relation to variation in GI and GL. Secondary outcome variables were HRs for CHD in relation to available carbohydrate, starch, and sugar. HRs with 95% CIs were estimated by Cox proportional hazard models using center-, age-, and sex-stratified baseline hazards.

Age was the time variable: participant entry was age at recruitment; exit was age at first CHD event, death for other causes, loss to follow-up, or end of CHD follow-up (whichever occurred first). Dietary intakes of interest were adjusted for energy intake using the regression-residual method (24) and categorized (quintiles) based on the entire cohort. Models were run on men and women together, with stratification by sex only in subgroup analyses. The study variables were also modeled as continuous variables, in which case HRs indicate risks associated with 50 g/d (GL) or 5 units/d (GI) increments of intake. Available carbohydrate was defined as starch and sugars; indigestible carbohydrate was excluded.

Three models are presented. Model 1 was stratified by center, age, and sex. Model 2 was additionally adjusted for smoking status (current: 1–15 cigarettes/d, 16–25 cigarettes/d, ≥26 cigarettes/d; former: quit ≤10 y, 11–20 y, ≥20 y previously; never), physical activity (inactive, moderately inactive, moderately active, active), BMI (<25, 25–29.9, ≥30), alcohol consumption (not drinker; sex-specific quintiles of intake—cut points in men: 4.1, 10.6, 19.6, and 37.5 g/d; cut points in women: 1.1, 3.4, 7.7, and 14.7 g/d), education (no schooling, primary, technical/professional, secondary, longer education), and blood pressure (high, normal, unknown/missing). Model 3 was additionally adjusted (all continuous) for intakes of energy, saturated fat, monounsaturated fat, protein, and fiber (or cereal fiber for the analyses investigating GI and GL). Model 3, analyzing GL and available carbohydrate, was also run adjusting for energy, polyunsaturated and monounsaturated fat (not saturated fat), protein, and fiber (or cereal fiber); another model 3 was run adjusting for energy, polyunsaturated and saturated monounsaturated fat (not protein), and fiber (or cereal fiber).

To assess the significance of trends, we employed orthogonal polynomial contrasts. Country-specific HRs for dietary GI and GL (continuous) were also estimated and combined with random-effects meta-analyses. Pooled HRs were then plotted, and between-country heterogeneity was quantified by the I^2 statistic (25). The proportional hazards assumption for all variables in relation to CHD risk was tested using the Grambsch and Therneau method (26). In all cases, the assumption was satisfied.

To assess whether dietary factors might act through circulating CHD risk factors, we performed ANCOVA to examine associations of GL/GI with biomarkers of CHD risk (CRP, HDL cholesterol, non-HDL cholesterol, triglycerides, glycated hemoglobin, glucose), calculating mean concentrations in each quintile of GL and adjusting for the covariates used in model 3. We also examined whether associations of CHD with dietary variables were influenced by reverse causality by excluding CHD events diagnosed in the first 2 y of follow-up.

TABLE 1 Baseline nutrient intakes and cardiovascular risk factors by quintiles of energy-adjusted dietary glycemic load in the EPIC cohort[1]

	Quintiles of energy-adjusted dietary GL[2]				
	I	II	III	IV	V
Participants, *n*	68,116	68,116	68,116	68,116	68,115
Dietary GL	96.5 ± 14.3	118.0 ± 3.7	129.5 ± 3.7	141.2 ± 3.8	164.8 ± 16.8
Dietary GI	53.4 ± 3.6	54.9 ± 3.2	55.8 ± 3.1	56.7 ± 3.1	58.3 ± 3.3
Protein, g/d	98.9 ± 30.2	84.6 ± 25.6	80.0 ± 25.4	78.8 ± 25.4	85.9 ± 27.4
Saturated fat, g/d	37.1 ± 14.4	31.2 ± 12.1	29.3 ± 11.7	28.4 ± 11.7	29.2 ± 12.2
Monounsaturated fat, g/d	42.1 ± 17.4	31.9 ± 12.6	28.3 ± 11.6	26.5 ± 11.4	28.1 ± 12.2
Polyunsaturated fat, g/d	15.5 ± 7.7	13.1 ± 6.0	12.5 ± 5.6	12.3 ± 5.6	13.0 ± 5.8
Carbohydrate, g/d	201.7 ± 63.5	203.8 ± 61.1	215.5 ± 61.2	237.1 ± 62.6	301.0 ± 79.5
Starch, g/d	104.1 ± 40.6	106.3 ± 39.1	113.3 ± 39.2	126.1 ± 41.0	166.2 ± 60.6
Sugars, g/d	90.5 ± 36.8	92.4 ± 35.9	98.2 ± 37.4	107.8 ± 40.7	132.1 ± 54.5
Fiber, g/d	21.5 ± 7.4	21.0 ± 6.9	21.7 ± 7.1	23.2 ± 7.4	27.5 ± 8.9
Energy, kcal/d	2303 ± 656	1997 ± 579	1939 ± 575	1979 ± 583	2287 ± 649
Alcohol, g/d	25.5 ± 27.1	14.0 ± 16.1	10.2 ± 12.8	8.12 ± 11.2	7.17 ± 10.8
Age, y	51.1 ± 9.3	51.4 ± 9.9	50.9 ± 10.6	49.9 ± 11.2	48.8 ± 11.4
Systolic blood pressure, mm Hg	132.2 ± 20.0	131.9 ± 19.8	131.2 ± 19.8	130.4 ± 19.8	129.4 ± 19.0
Diastolic blood pressure, mm Hg	82.2 ± 10.8	81.5 ± 10.8	81.0 ± 10.8	80.6 ± 10.8	80.2 ± 10.7
BMI, kg/m^2	26.7 ± 4.30	26.2 ± 4.32	25.8 ± 4.26	25.4 ± 4.16	25.1 ± 4.08
Sex					
Male, %	47.8	33.1	29.3	30.2	40.5
Physical activity, %					
Inactive	23.2	22.4	20.8	19.5	20.5
Moderately inactive	33.5	33.9	33.9	33.4	30.9
Moderately active	23.3	22.9	23.3	23.7	23.1
Active	19.5	19.7	20.5	21.6	23.2
Education, %					
No schooling	7.2	6.7	5.7	4.4	3.3
Primary	30.6	29.1	27.2	25.4	27.4
Technical/professional	21.9	24.8	25.8	26.0	24.4
Secondary	14.4	14.3	14.7	16.3	17.8
Longer education	24.8	23.3	24.0	24.8	23.4
Current smoker, %	34.6	26.1	22.5	20.2	21.3
Never smoker, %	36.7	46.3	50.1	53.0	52.3
History of high blood pressure, %	34.8	34.7	33.7	32.0	29.8

[1]Values are means ± SDs, except where indicated. EPIC, European Prospective Investigation into Cancer and Nutrition; GI, glycemic index; GL, glycemic load.

[2]Energy adjustment by residual method.

To examine whether associations of CHD with dietary variables were consistent across subgroups of other risk factors, we conducted subgroup analyses by sex and BMI. Tests for heterogeneity of trend were performed adding appropriate interaction terms to the models and testing for significance using a Wald chi-square test. All analyses were conducted using Stata software (version 14.0; StataCorp).

Results

After 12.8 y (median), 6378 incident CHD cases (4267 men, 2111 women) were identified in the EPIC cohort. **Table 1** shows baseline characteristics of the cohort by quintiles of energy-adjusted dietary GL. Mean GL varied substantially across quintiles (range: 96.5–164.8), and mean GI ranged from 53.4 (lowest quintile) to 58.3 (highest quintile). Participants in the highest GL quintile consumed more carbohydrate and starch and less fat, protein, and alcohol, and they had lower BMI, compared with those in the lowest quintile; they were often more active and less often current smokers.

Table 2 shows cohort characteristics by quintiles of energy-adjusted dietary GI. Mean GI ranged from 50.7 (lowest quintile) to 60.8 (highest quintile); GL ranged from 113.7 (lowest quintile) to 146.6 (highest quintile). Those in the highest GI quintile consumed less saturated fat, monounsaturated fat, and protein, and consumed more carbohydrate and starch, compared with in lower quintiles; they were also less educated and more often smokers. Fiber intake and sugar intake increased with increasing GL but decreased with increasing GI.

Table 3 shows baseline means of selected biomarkers by quintiles of energy-adjusted GL and GI. Those in the highest GL and GI quintiles had significantly lower HDL cholesterol compared with those in the lowest quintiles; those in the highest GI quintile had significantly higher triglycerides and CRP compared with those in the lowest quintile.

Table 4 shows HRs for CHD by quintiles of energy-adjusted GL, GI, available carbohydrate, starch, and sugar. In models 1 (minimally adjusted) and 2 (adjusted for CHD risk factors), CHD risk was unrelated to GL. After adjusting for nutrient intake (model 3), the 4th and 5th GL quintiles were associated

TABLE 2 Baseline nutrient intakes and cardiovascular risk factors by quintiles of energy-adjusted dietary glycemic index in the EPIC cohort[1]

	Quintiles of energy-adjusted[2] dietary GI				
	I	II	III	IV	V
Participants, *n*	68,116	68,116	68,116	68,116	68,115
Dietary GI	50.7 ± 2.14	54.0 ± 0.57	55.8 ± 0.49	57.6 ± 0.59	60.8 ± 1.81
Dietary GL	113.7 ± 22.7	124.0 ± 20.5	129.9 ± 20.9	135.7 ± 21.5	146.6 ± 26.0
Protein, g/d	87.5 ± 29.0	86.3 ± 27.5	85.4 ± 27.1	84.6 ± 26.9	84.6 ± 28.4
Saturated fat, g/d	31.9 ± 13.9	32.0 ± 12.9	31.5 ± 12.6	30.8 ± 12.4	29.0 ± 12.2
Monounsaturated fat, g/d	32.9 ± 16.8	32.0 ± 14.7	31.3 ± 13.9	30.7 ± 13.2	30.1 ± 12.9
Polyunsaturated fat, g/d	13.1 ± 6.6	13.5 ± 6.3	13.5 ± 6.2	13.3 ± 6.1	13.1 ± 6.2
Carbohydrate, g/d	222.1 ± 77.4	230.7 ± 73.0	233.0 ± 72.9	234.1 ± 73.8	239.2 ± 79.2
Starch, g/d	98.0 ± 40.8	115.3 ± 42.5	123.5 ± 44.9	130.8 ± 48.0	148.3 ± 59.2
Sugar, g/d	118.4 ± 49.5	110.2 ± 43.0	104.9 ± 41.5	99.2 ± 41.1	88.4 ± 40.1
Fiber, g/d	23.2 ± 8.5	23.4 ± 7.9	23.2 ± 7.8	22.8 ± 7.7	22.4 ± 7.8
Energy, kcal/d	2093 ± 658	2118 ± 627	2110 ± 618	2095 ± 613	2090 ± 633
Alcohol, g/d	13.8 ± 19.6	13.2 ± 17.3	12.9 ± 17.3	12.6 ± 17.5	12.4 ± 18.4
Age, y	50.4 ± 10.1	50.6 ± 10.5	50.5 ± 10.8	50.4 ± 10.9	50.1.3 ± 9.3
Systolic blood pressure, mm Hg	130.0 ± 19.5	131.0 ± 19.5	131.5 ± 19.8	131.5 ± 20.0	130.9 ± 19.8
Diastolic blood pressure, mm Hg	81.0 ± 10.6	81.2 ± 10.7	81.2 ± 10.8	81.1 ± 10.9	81.0 ± 10.9
BMI, kg/m^2	26.1 ± 4.35	25.8 ± 4.25	25.7 ± 4.20	25.7 ± 4.22	25.9 ± 4.29
Sex					
Male (%)	27.3	32.6	36.3	39.3	45.3
Physical activity, %					
Inactive	20.0	19.4	20.4	21.5	25.0
Moderately inactive	33.9	34.1	33.3	32.9	31.4
Moderately active	23.6	24.0	23.9	23.2	21.5
Active	21.9	21.8	21.2	20.6	18.8
Education, %					
No schooling	5.3	4.3	4.8	5.3	7.5
Primary	26.6	25.6	26.3	28.7	32.8
Technical/professional	25.4	25.1	24.8	24.1	23.2
Secondary	14.8	15.1	15.6	15.9	16.2
Longer education	26.2	27.0	25.7	23.2	18.2
Current smoker, %	23.5	22.1	23.1	25.3	30.6
Never smoker, %	48.7	50.0	46.2	47.2	43.1
History of high blood pressure, %	32.0	33.1	33.1	33.6	33.2

[1]Values are means ± SDs, except where indicated. EPIC, European Prospective Investigation into Cancer and Nutrition; GI, glycemic index; GL, glycemic load.

[2]Energy adjustment by residual method.

with greater CHD risk, with *P*-trend = 0.035. For 50 g/d GL increments, the HR was 1.18 (95% CI: 1.07, 1.29). In this model, in which the only nutrients not included were polyunsaturated and low-GI carbohydrate, the GL variable represents the effect of substituting GL for polyunsaturated fat and low-GI carbohydrate on CHD risk. When the adjustments in model 3 included polyunsaturated and monounsaturated fat (not saturated fat), the HR for 50 g/d GL increments was 1.19 (95% CI: 1.09, 1.29). When the adjustments in model 3 included polyunsaturated, monounsaturated, and saturated fat (not protein), the HR for 50 g/d GL increments was 1.13 (95% CI: 1.04, 1.23) (data not shown in tables).

GI was associated with greater CHD risk only in the continuous GI model [HR: 1.04 (95% CI: 1.00, 1.08) per 5 unit/d increment].

For available carbohydrate in model 3, those in the highest quintile of consumption had greater CHD risk compared with those in the lowest quintile (HR: 1.15; 95% CI: 1.00, 1.32; *P*-trend = 0.065); the HR for 50 g/d GL increments was 1.11 (95% CI: 1.03, 1.18). When model 3 was run adjusting for polyunsaturated fat, monounsaturated fat, and protein (not saturated fat), the HR for 50 g/d increments was 1.14 (95% CI: 1.07, 1.22); when run adjusting for polyunsaturated, monounsaturated, and saturated fat (not protein), the HR for 50 g/d increments was 1.08 (95% CI: 1.02, 1.15) (data not shown in tables). Sugar intake was associated with greater CHD risk in all quintiles of consumption, and the HR for 50 g/d increments was 1.09 (95% CI: 1.02, 1.17). Starch was not associated with CHD risk.

Estimates of country-specific HRs (data pooled from centers) with corresponding I^2 for between-country heterogeneity are shown in **Figure 1**. Associations of dietary variables with CHD risk did not vary greatly across countries.

Table 5 shows sensitivity analyses for GL/GI after excluding cases diagnosed in the first 2 y and also by sex and BMI. Associations between GL/GI and CHD attenuated after excluding those with an early CHD event during the first 2 y of follow-up [HR for 50 g/d intake: 1.15 (95% CI: 1.04, 1.27) for GL and 1.03 (95% CI: 0.99, 1.08) for GI].

TABLE 3 Mean values of selected markers of lipid and glucose metabolism (with 95% CIs) in the EPIC-CVD subcohort according to quintiles of energy-adjusted dietary glycemic index and glycemic load[1]

	Quintiles of energy-adjusted dietary GI or GL					
	I	II	III	IV	V	*P* value[2]
Dietary GL						
Non-HDL cholesterol, mmol/L	4.41 (4.35, 4.46)	4.39 (4.35, 4.43)	4.44 (4.40, 4.48)	4.47 (4.43, 4.51)	4.47 (4.41, 4.53)	0.1155
HDL cholesterol, mmol/L	1.54 (1.52, 1.56)	1.50 (1.49, 1.52)	1.48 (1.47, 1.50)	1.47 (1.46, 1.48)	1.46 (1.44, 1.48)	<0.001
Triglycerides, mmol/L	1.32 (1.28, 1.36)	1.28 (1.25, 1.32)	1.34 (1.31, 1.37)	1.35 (1.31, 1.38)	1.35 (1.31, 1.39)	0.0878
C-reactive protein, mg/L	2.06 (1.86, 2.25)	2.16 (2.01, 2.31)	2.30 (2.15, 2.45)	2.27 (2.11, 2.42)	2.37 (2.17, 2.58)	0.3424
Glucose, mmol/L	4.94 (4.88, 4.99)	4.92 (4.87, 4.96)	4.92 (4.88, 4.96)	4.94 (4.89, 4.98)	4.96 (4.90, 5.03)	0.7453
HbA1c, %	5.46 (5.44, 5.49)	5.47 (5.45, 5.49)	5.47 (5.46, 5.49)	5.49 (5.47, 5.50)	5.48 (5.46, 5.50)	0.6893
Dietary GI						
Non-HDL cholesterol, mmol/L	4.39 (4.35, 4.43)	4.39 (4.35, 4.43)	4.46 (4.42, 4.50)	4.44 (4.40, 4.48)	4.49 (4.45 4.53)	0.0055
HDL cholesterol, mmol/L	1.51 (1.49, 1.52)	1.50 (1.49, 1.52)	1.48 (1.47, 1.50)	1.48 (1.47, 1.50)	1.49 (1.47, 1.50)	0.0423
Triglycerides, mmol/L	1.32 (1.29, 1.35)	1.28 (1.25, 1.31)	1.33 (1.30, 1.36)	1.32 (1.29, 1.36)	1.38 (1.35, 1.41)	0.0011
C-reactive protein, mg/L	2.08 (1.92, 2.23)	2.15 (2.00, 2.30)	2.22 (2.07, 2.36)	2.28 (2.13, 2.42)	2.43 (2.28, 2.59)	0.0340
Glucose, mmol/L	4.95 (4.90, 4.99)	4.91 (4.87, 4.96)	4.93 (4.88, 4.97)	4.93 (4.88, 4.97)	4.95 (4.90, 5.00)	0.6923
HbA1c, %	5.47 (5.45, 5.49)	5.47 (5.45, 5.49)	5.48 (5.46, 5.50)	5.48 (5.46, 5.49)	5.48 (5.46, 5.49)	0.8679

[1]Means adjusted for age (continuous); sex; EPIC center; smoking; education; physical activity; BMI; blood pressure; and intakes of energy, protein, alcohol, fiber, and saturated and monounsaturated fat. CVD, cardiovascular disease; EPIC, European Prospective Investigation into Cancer and Nutrition; GI, glycemic index; GL, glycemic load; HbA1c, glycated hemoglobin.

[2]ANCOVA.

Model 3 HR estimates for each sex were in the same direction as for the sexes combined. GL was significantly associated with CHD risk in both sexes [HR for 50 g/d intake: 1.19 (95% CI: 1.08, 1.30) for men and 1.22 (95% CI: 1.07, 1.40) for women], whereas GI was significantly associated only in women [HR for 50 g/d intake: 1.09 (95% CI: 1.02, 1.16) for women and 1.02 (95% CI: 0.98, 1.07) for men]. However, the interaction of dietary GL and GI with sex was not significant.

Finally, associations between CHD and GL varied with BMI category. High GL was associated with greater CHD risk among participants with BMI ≥25 (HR for 50 g/d increments: 1.22; 95% CI: 1.11, 1.35), whereas no association was found in participants with BMI <25 (HR for 50 g/d increments: 1.09; 95% CI: 0.96, 1.22). The interaction of GL with BMI was significant ($P = 0.022$).

Discussion

In this prospective study with 6378 incident CHD cases from 8 European countries, high dietary GL and GI were associated with greater CHD risk. Dietary GL was also significantly associated with greater CHD risk in overweight and obese persons, but not in those of normal weight. High consumption of carbohydrate and sugar, but not starch, was also associated with greater CHD risk.

Three meta-analyses of cohort studies (8–11) found that high dietary GL was significantly associated with increased CHD risk, whereas high dietary GI was inconsistently associated with risk, and the risk increases were significant only in women (when the sexes were analyzed separately). However, some studies that found (non significant) risk increases in men (27, 28) were not included in the meta-analyses because the data were unavailable in suitable form. When we analyzed men and women separately, HR estimates for dietary GL were in the same direction as those for both sexes combined. A 2019 meta-analysis (that only included prospective studies in which the correlation between carbohydrate intake from questionnaires and ascertained food records was >0.55) found a strong relation between GL and CHD risk that did not vary between men and women (12). Finally, a large and comprehensive review and meta-analysis, also published in 2019, that used the Grading of Recommendations Assessment, Development, and Evaluation approach to assess evidence quality reported a moderate positive association, across observational studies, of GL with CHD endpoints (mortality and incidence) (13).

We found a weak positive association between dietary GI and CHD only in the continuous model. When we analyzed men and women separately, HR estimates for dietary GI were in the same direction as those for both sexes combined, although the association was significant only in women, but test for interaction was not significant.

Three previous meta-analyses showed that a high GI diet was significantly associated with CHD events in women but not men (8, 9, 11). However, a recent large and comprehensive review and meta-analysis reported a null or inconsistent finding for GI across observational studies for CHD endpoints (13).

CHD risk in relation to available carbohydrate consumption has also been examined in prospective studies but with inconsistent results: a positive association was found in both sexes that consumed carbohydrate mainly from white rice and refined wheat products (29), whereas other studies found no associations in women (30, 31) or men (32). The Prospective Urban Rural Epidemiology study found that high carbohydrate intake was associated with increased risk of total mortality but not with the risk of CVD (33).

Regarding our finding of a greater risk of CHD with high sugar consumption, few studies have investigated this association. The Nurses' Health Study and the Women's Health Initiative Observational Study found that sugar intake was not significantly related to CHD risk (30, 34). Moreover, a recent meta-analysis of prospective studies found that neither total sugar nor sucrose was associated with CVD incidence, either in extreme quantile analyses or in linear and nonlinear dose–response models (35).

TABLE 4 HRs (with 95% CIs) for first coronary heart disease event according to dietary glycemic load, dietary glycemic index, and intakes of available carbohydrate, starch, and sugar in the EPIC study[1]

	Quintiles of energy-adjusted dietary variables						
	I	II	III	IV	V	*P*-trend[2]	Continuous[3]
Dietary GL							
Range	≤111.2	111.3–124.1	124.2–134.9	135.0–148.3	>148.3		
Cases, *n*	1386	1255	1175	1208	1354		
Model 1[4]	1	1.02 (0.94, 1.10)	1.00 (0.92, 1.08)	1.01 (0.93, 1.10)	1.05 (0.96, 1.14)	0.373	1.04 (0.99, 1.10)
Model 2[5]	1	1.05 (0.97, 1.14)	1.02 (0.94, 1.11)	1.04 (0.96, 1.14)	1.06 (0.97, 1.16)	0.248	1.05 (1.00, 1.11)
Model 3[6,7]	1	1.08 (0.99, 1.17)	1.07 (0.97, 1.17)	1.11 (1.00, 1.23)	1.16 (1.02, 1.31)	0.035	1.18 (1.07, 1.29)
Dietary GI							
Range	≤52.9	53.0–54.9	55.0–56.7	56.8–58.7	>58.7		
Cases, *n*	958	1054	1265	1395	1706		
Model 1[4]	1	0.97 (0.89, 1.06)	1.05 (0.96, 1.14)	1.06 (0.97, 1.15)	1.17 (1.08, 1.27)	0.001	1.09 (1.05, 1.13)
Model 2[5]	1	0.98 (0.90, 1.07)	1.04 (0.96, 1.14)	1.02 (0.93, 1.11)	1.05 (0.96, 1.14)	0.172	1.03 (0.99, 1.07)
Model 3[6,7]	1	1.00 (0.91, 1.09)	1.07 (0.98, 1.16)	1.04 (0.95, 1.13)	1.08 (0.99, 1.18)	0.053	1.04 (1.00, 1.08)
Available carbohydrate							
Range	≤202.0	202.0–222.9	223.0–240.4	240.5–261.5	>261.5		
Cases, *n*	1542	1250	1206	1145	1235		
Model 1[4]	1	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)	0.94 (0.87, 1.02)	1.00 (0.92, 1.08)	0.701	1.00 (0.97, 1.03)
Model 2[5]	1	1.02 (0.94, 1.10)	1.02 (0.94, 1.11)	1.00 (0.92, 1.09)	1.06 (0.97, 1.15)	0.355	1.03 (0.99, 1.06)
Model 3[6]	1	1.04 (0.96, 1.14)	1.06 (0.96, 1.17)	1.06 (0.95, 1.19)	1.15 (1.00, 1.32)	0.065	1.11 (1.03, 1.18)
Starch							
Range	≤97.4	97.5113.3	113.4127.7	127.8147.0	>147.0		
Cases, *n*	1355	1224	1205	1322	1272		
Model 1[4]	1	0.95 (0.88, 1.03)	0.90 (0.83, 0.97)	0.92 (0.85, 1.00)	0.86 (0.79, 0.93)	0.001	0.93 (0.90, 0.97)
Model 2[5]	1	0.99 (0.91, 1.07)	0.95 (0.87, 1.03)	0.97 (0.90, 1.05)	0.93 (0.85, 1.02)	0.116	0.98 (0.94, 1.02)
Model 3[6,8]	1	1.02 (0.94, 1.11)	0.99 (0.90, 1.09)	1.04 (0.93, 1.15)	1.02 (0.89, 1.16)	0.737	1.06 (0.99, 1.14)
Sugar							
Range	≤77.2	77.3,93.5	93.6108.8	108.9129.3	>129.3		
Cases, *n*	1509	1306	1200	1181	1182		
Model 1[4]	1	1.05 (0.97, 1.13)	1.05 (0.97, 1.13)	1.07 (0.99, 1.16)	1.13 (1.04, 1.23)	0.006	1.05 (1.01, 1.09)
Model 2[5]	1	1.09 (1.01, 1.18)	1.09 (1.01, 1.18)	1.12 (1.03, 1.21)	1.13 (1.04, 1.23)	0.007	1.04 (1.00,1.08)
Model 3[6,8]	1	1.12 (1.03, 1.22)	1.14 (1.04, 1.24)	1.18 (1.07, 1.31)	1.24 (1.09, 1.40)	0.001	1.09 (1.02, 1.17)

[1]HRs and 95% CIs estimated from Cox proportional hazard models. EPIC, European Prospective Investigation into Cancer and Nutrition; GI, glycemic index; GL, glycemic load.

[2]Interquintile test for trend calculated by orthogonal polynomial contrasts.

[3]For 50 g/d increments of dietary GL, carbohydrate, starch, and sugar or 5 units/d increments of dietary GI.

[4]Stratified by age, sex, and recruitment center.

[5]Additionally adjusted for smoking, education, physical activity, BMI, and blood pressure variable.

[6]Additionally adjusted for intakes of energy, protein, alcohol, fiber, and saturated and monounsaturated fat.

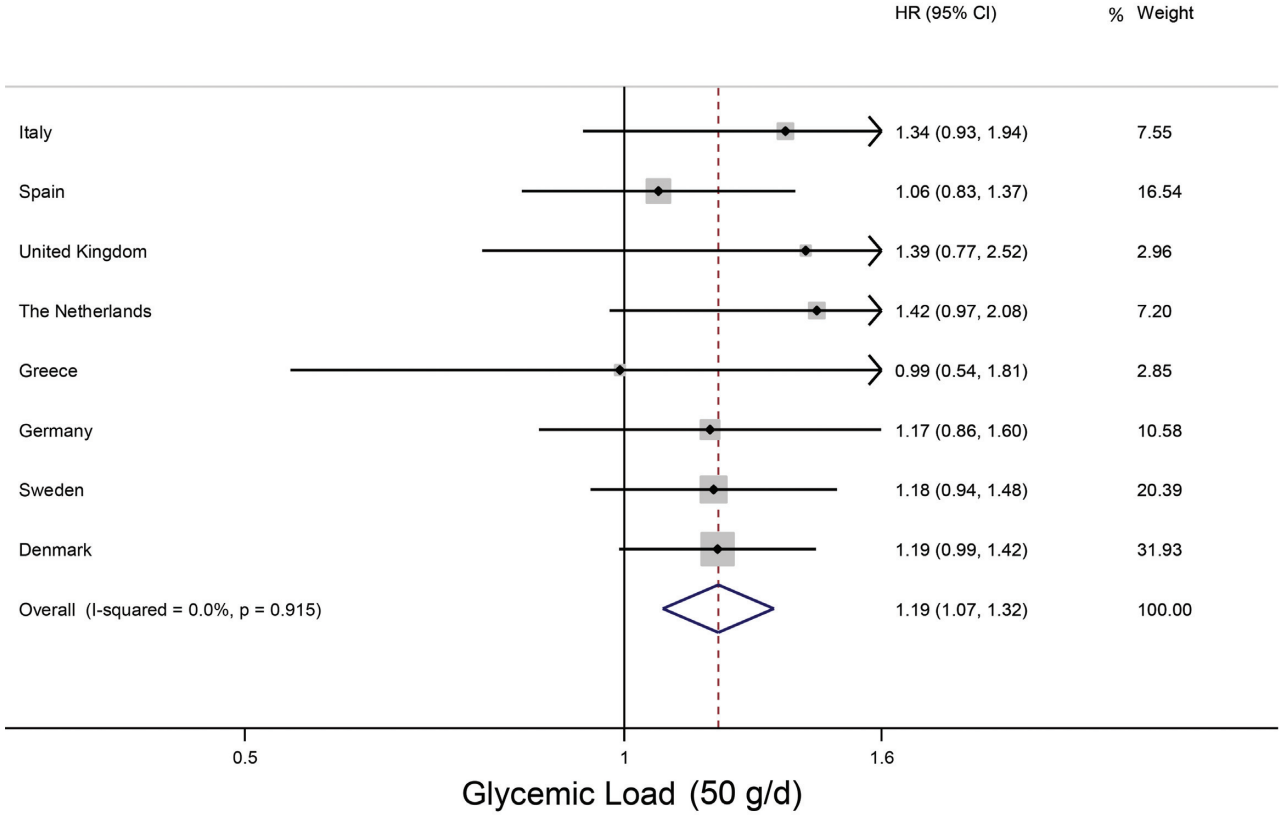
[7]Models 3 for GL and GI were adjusted for cereal fiber instead of fiber.

[8]Models 3 for sugar and for starch were adjusted for starch and sugar, respectively.

Many other studies have evaluated the relation of sugars in the form of sugar-sweetened beverages (SSBs) to CHD. A meta-analysis of cohort studies reported that intake of SSBs was associated with CHD risk (36). More recently, data from the Nurses' Health Study and the Health Professionals Follow-Up Study reaffirmed a strong positive association between foods rich in refined starches and added sugars and CHD risk (37). These findings are consistent with the results of randomized trials which indicate that high sugar increases blood pressure and also blood triglycerides, total cholesterol, and LDL cholesterol (38).

It is important to note that the association between dietary GL and CHD risk was evident in our study only after adjustment for dietary variables (model 3). Like most previous studies (30, 39–42), we found that high dietary GL was associated with high fiber intake and low saturated fat and protein intake. So, it is reasonable that associations of dietary GL with CHD risk only became significant after additional adjustment for these variables, even though such adjustments can be considered overadjustments because fiber, fat, and protein in foods influence their GI/GL. Furthermore, the strength of the GL–CHD association did not change when the substitution of GL for polyunsaturated or saturated fat or protein was evaluated. A randomized controlled trial that investigated CHD in relation to replacing dietary fat with carbohydrates found no risk change (43). We also found that replacing dietary fat (saturated or polyunsaturated fat) or protein with carbohydrate was associated with greater CHD risk.

Our findings are in line with those of a meta-analysis of 6 observational studies (9) which found that persons with higher BMI, who consumed a high GL diet, were at greater risk of CHD, so body weight may serve as an effect modifier on this association. The Nurses' Health Study was the first to report that in women with high BMI (>23), the risk of CHD increased as intake of high-GI foods increased (30).



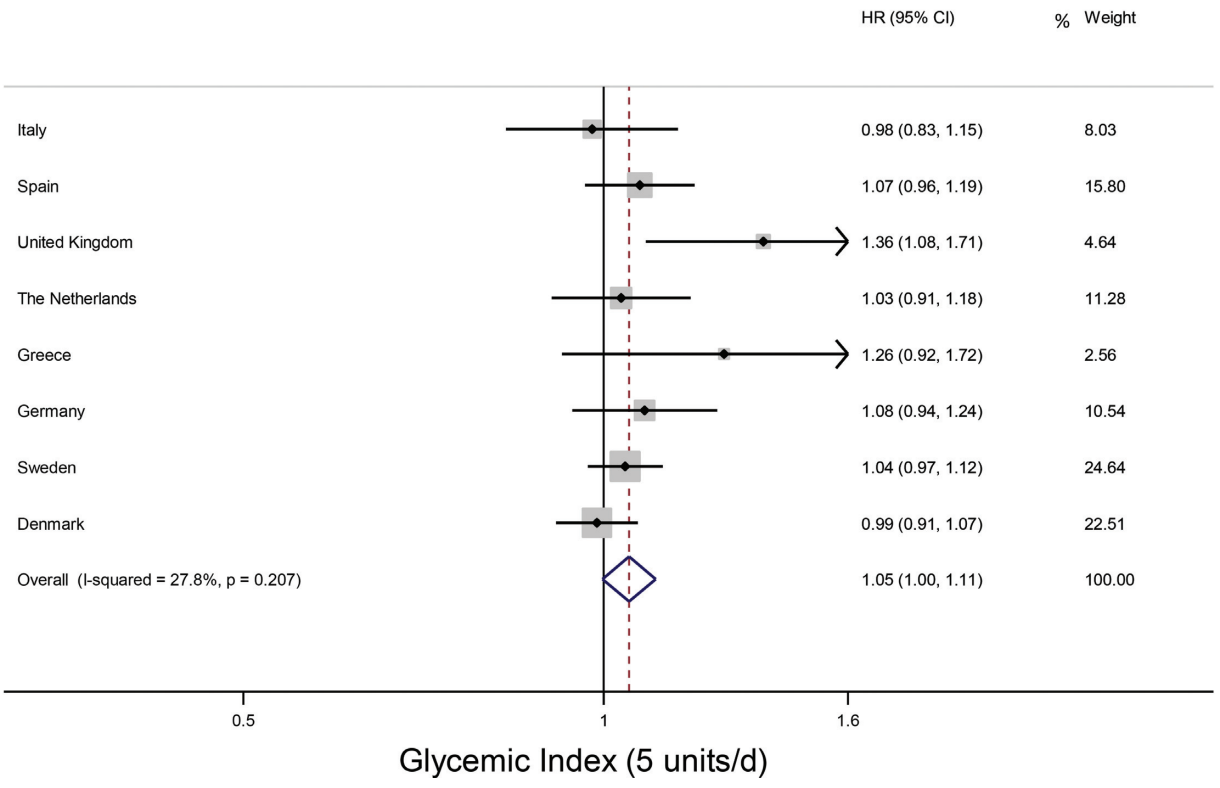
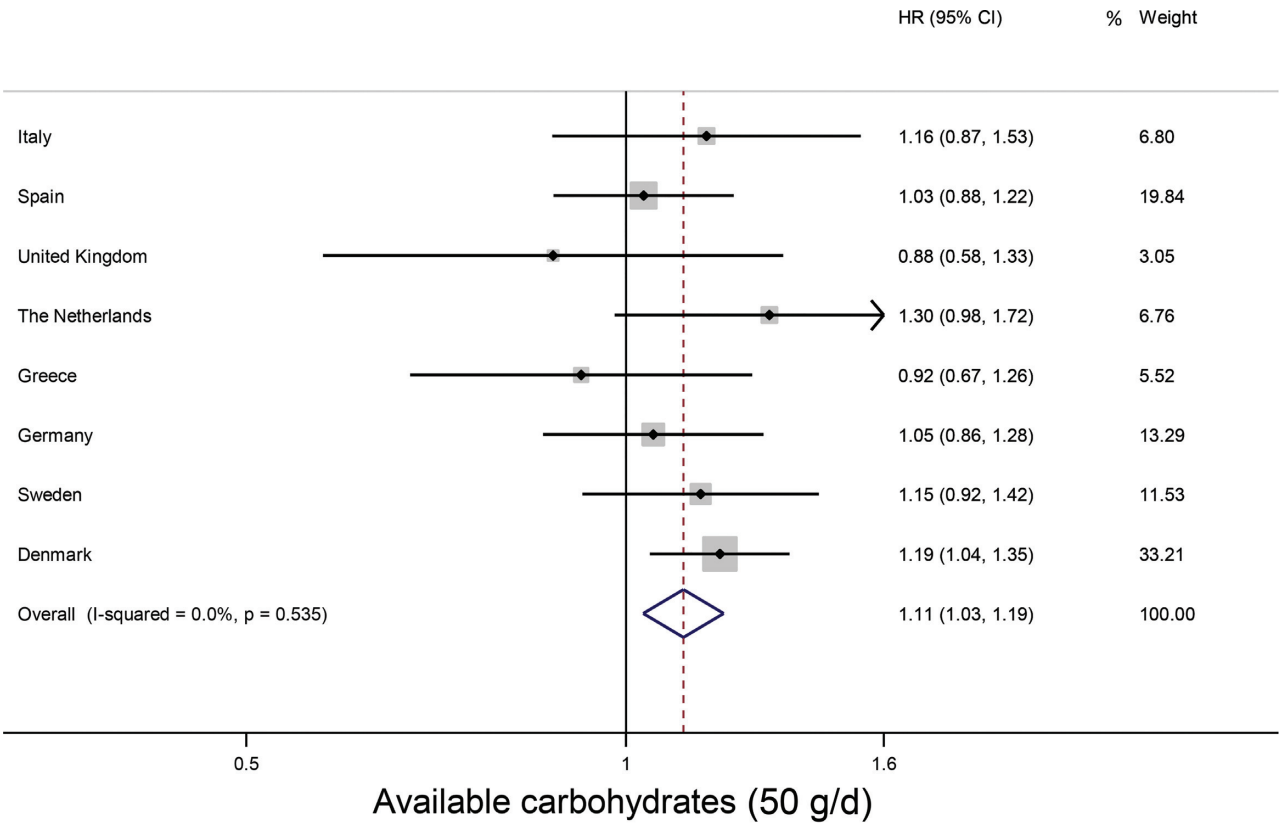


FIGURE 1 *Continued.*



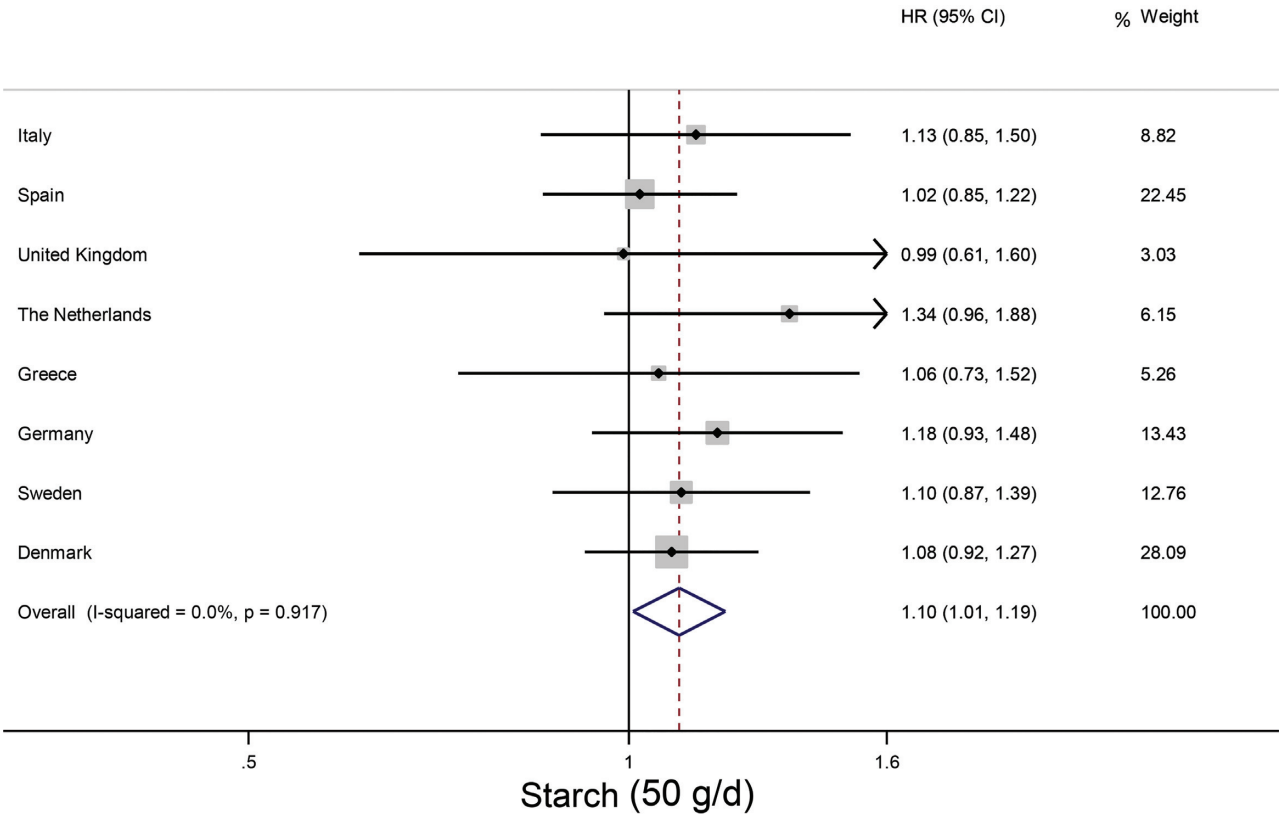


FIGURE 1 *Continued.*

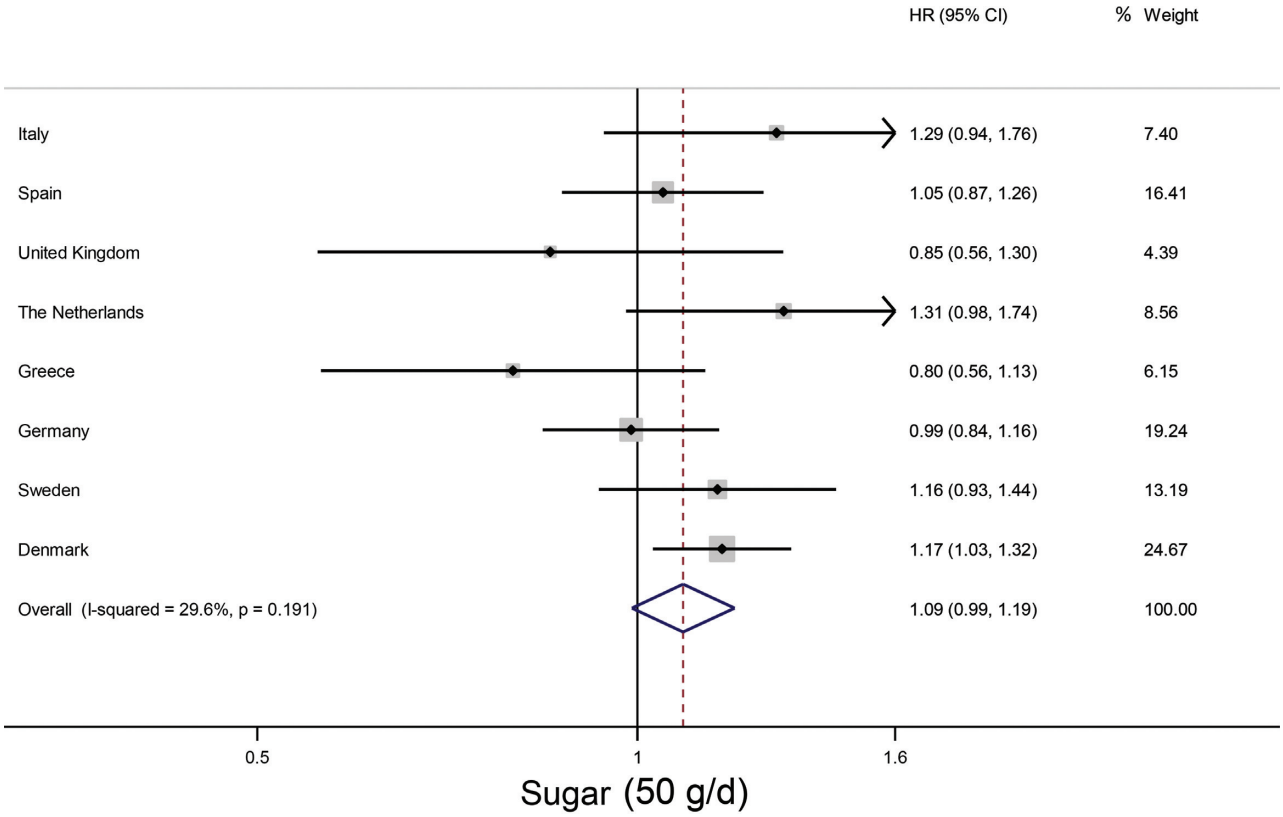


FIGURE 1 Forest plots showing country-specific HRs and 95% CIs for coronary heart disease in relation to dietary glycemic load; dietary glycemic index; and intakes of available carbohydrate, starch, and sugar. The HRs were obtained from model 3, which was adjusted for age; sex; study center; smoking; education; physical activity; BMI; blood pressure; and intakes of energy, protein, alcohol, fiber (available carbohydrate, starch, and sugar), cereal fiber (GI and GL), and saturated and monounsaturated fat. The analyses were stratified by country and combined with random-effects meta-analysis. Weights are from random-effects analysis.

The mediators of the association of high carbohydrate intake with increased CHD risk are not completely understood, but it is likely that insulin resistance is involved. A high-carbohydrate meal (particularly of high GI carbohydrate) substantially increases postprandial blood glucose and insulin. The subsequent insulin-induced decline in blood glucose precipitates hunger within a few hours, stimulating further consumption (of typically high-GI foods) so that blood glucose remains elevated over a prolonged period (44). If such behavior is habitual, it may lead to insulin resistance and obesity (45, 46), with increased triglycerides and LDL cholesterol and lowered HDL, leading to metabolic syndrome.

Hyperinsulinemia and hyperglycemia may also trigger peripheral vasoconstriction, sodium retention, and increased liver production of VLDL, leading to atherosclerosis (47). In people with high BMI, greater insulin demand in response to a high-GL diet may further exacerbate insulin resistance and lipid imbalance, thereby increasing CHD risk (48). This scenario is supported by a meta-analysis of randomized intervention trials (49) which found that lowering dietary GI reduced CVD risk factors, lowering triglycerides and LDL cholesterol and raising HDL cholesterol. However, such responses are not always observed (50, 51). From Table 3 it is evident that as dietary GI increased, so did triglyceride and non-HDL cholesterol concentrations, whereas as dietary GL increased, HDL cholesterol decreased. These cross-sectional associations are nevertheless consistent with the hypothesis that insulin resistance mediates the high carbohydrate–CHD association. A randomized intervention trial on patients with diabetes found higher HDL cholesterol concentrations in the low-GI treatment group (52).

Strengths of our study are the large number of CHD cases, the prospective design, and the long follow-up, limiting the likelihood of reverse causation and selection bias. Although we had extensive data on potential confounders that were used as covariates in the models, we cannot rule out the presence of residual confounding.

A limitation of our study is that the dietary questionnaires (14) were not designed to specifically estimate dietary GI/GL, although application of GI values to food items is straightforward, and Liu et al. found it was possible to accurately estimate dietary GI and GL from questionnaire responses (53). Another limitation is that diet was only assessed at baseline. Some participants may have changed their diet during follow-up, giving rise to misclassification of exposure, which would have weakened diet–disease associations. Finally, most people do not eat single foods but, rather, meals, and a food's GI can vary depending on how it is prepared and combined with other foods. It is not possible to take such interactions into account using a food questionnaire. However, strong correlations have

TABLE 5 Subgroup analyses: HRs (with 95% CIs) for first coronary heart disease event according to quintiles of dietary glycemic load and glycemic index in the EPIC study[1]

	Quintiles of energy-adjusted dietary GL or GI						
	I	II	III	IV	V	*P*-trend[2]	Continuous[3]
Dietary GL							
Excluding cases diagnosed in the first 2 y (5648 cases)							
Model 3[4,5]	1	1.05 (0.96, 1.15)	1.00 (0.91, 1.11)	1.07 (0.95, 1.19)	1.10 (0.97, 1.26)	0.186	1.15 (1.04, 1.27)
Men only (4251 cases)							
Model 3[4]	1	1.07 (0.97, 1.18)	1.08 (0.97, 1.20)	1.13 (1.01, 1.27)	1. 17 (1.02, 1.34)	0.027	1.19 (1.08, 1.30)
Women only (2103 cases)							
Model 3[4]	1	1.12 (0.96, 1.30)	1.11 (0.96, 1.30)	1.14 (0.97, 1.34)	1.23 (1.02, 1.47)	0.062	1.22 (1.07, 1.40)
P heterogeneity							0.588
According to BMI, kg/m^2							
<25 (2025 cases)							
Model 3[4,5]	1	0.94 (0.81, 1.09)	0.90 (0.78, 1.05)	0.99 (0.85, 1.16)	0.98 (0.83, 1.16)	0.984	1.09 (0.96, 1.22)
≥25 (4329 cases)							
Model 3[4,5]	1	1.14 (1.03, 1.26)	1.15 (1.03, 1.28)	1.16 (1.03, 1.31)	1.26 (1.10, 1.44)	0.004	1.22 (1.11, 1.35)
P heterogeneity							0.022
Dietary GI							
Excluding cases diagnosed in the first 2 y (5648 cases)							
Model 3[4,5]	1	0.98 (0.89, 1.07)	1.05 (0.96, 1.15)	1.04 (0.95, 1.14)	1.05 (0.96, 1.16)	0.115	1.03 (0.99, 1.08)
Men only (4251 cases)							
Model 3[4]	1	0.94 (0.84, 1.05)	0.98 (0.88, 1.09)	0.99 (0.89, 1.11)	1.01 (0.91, 1.12)	0.396	1.02 (0.98, 1.07)
Women only (2103 cases)							
Model 3[4]	1	1.11 (0.97, 1.28)	1.24 (1.08, 1.42)	1.11 (0.96, 1.28)	1.22 (1.06, 1.40)	0.014	1.09 (1.02, 1.16)
P heterogeneity							0.090
According to BMI, kg/m^2							
<25 (2025 cases)							
Model 3[4,5]	1	1.03 (0.88, 1.21)	0.99 (0.85, 1.16)	1.00 (0.86, 1.16)	1.04 (0.90, 1.21)	0.686	1.03 (0.97, 1.10)
≥25 (4329 cases)							
Model 3[4,5]	1	0.98 (0.88, 1.09)	1.10 (0.99, 1.22)	1.06 (0.96, 1.18)	1.10 (0.99, 1.22)	0.026	1.05 (1.00, 1.10)
P heterogeneity							0.674

[1]HRs and 95% CIs estimated from Cox proportional hazard models. EPIC, European Prospective Investigation into Cancer and Nutrition; GI, glycemic index; GL, glycemic load.

[2]Interquintile test for trend calculated by orthogonal polynomial contrasts.

[3]For 50 g/d increments of dietary GL or 5 units/d increments of dietary GI.

[4]Stratified by age and recruitment center and adjusted for smoking, education, physical activity, BMI, blood pressure variable, and intakes of energy, protein, alcohol, cereal fiber, and saturated and monounsaturated fat.

[5]Additionally stratified by sex.

been found between observed and calculated GIs for mixed meals (54).

In conclusion, this large pan-European study has revealed a robust positive association between a diet that induces a high glucose response and increased CHD risk.

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The authors' responsibilities were as follows—SS, VK, CA, SG, JD, and ASB: designed the study, had full access to all study data, and take responsibility for the integrity of the data and the accuracy of the analyses; SS: drafted the manuscript; SS and VK: performed the statistical analyses; SG, EW, AM, IS, MUJ, MS, YTvdS, LMN, PW, VAK, TK, KO, TYNT, M-IC, JRQ, JMG-T, OM, J-HG, A Tjønneland, ES, A Trichopoulou, AK, EV, JMAB, WMMV, MJF, M-CB-R, GF, A-LM, MMB, MBS, PF, HF, HL, CS, GM, RT, ER, JD, ASB, NGF, NJW, and VK; take responsibility for the databases and follow-up data; and all authors: contributed to data interpretation and critical revision of the manuscript, and read and approved the final manuscript. ASB has received grants unrelated to the current study from AstraZeneca, Biogen, Merck, Novartis, and Sanofi. All other authors report no conflicts of interest.

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